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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,858	12/14/2001	Karen Koch	6225.200-US	7430

23650 7590 05/17/2004

NOVO NORDISK PHARMACEUTICALS, INC
100 COLLEGE ROAD WEST
PRINCETON, NY 08540

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,858	KOCH ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,40,43,45-47 and 49-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35, 36, 40, 43, 45-47, and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and the declaration by Dr. Nachtigall filed February 25, 2004 have been entered.

Claims 35, 36, 40, 43, 45-47, and 49-53 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 35, 36, 40, 43, 45-47, and 49-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meignant (US Patent 6,060,077) in view of Mettler and Olsen and Vagifem monograph, all references are of record.

Meignant teaches the employment of low dose 17-β-estradiol, i.e., 5μg or 2.5μg, locally to treat atrophic vaginitis (See col. 4, lines 27-36; also col. 6, lines 38-54). Meignant teaches the dosage frequency can be adjusted to avoid the systemic effects

(See col. 4, lines 23-25). Please note that the lowering of the vaginal pH is considered as a result from the exact same active method steps herein (See McCane, reference of record).

Meignant does not expressly teach the dosage form of the medicament as tablet that contains 53.7mg hypromellose, about 17.9mg lactose monohydrate, about 8 mg maize starch, and about 0.4 mg magnesium stearate. Meignant does not expressly teach the tablet is coated with a film consisting of about 0.5mg hypromellose and about 0.06 mg Macrogel 6000. Meignant does not expressly teach estradiol is administered once or twice weekly.

Mettler and Olsen teaches a method of treating atrophic vaginitis by vaginally administering 25μg tablets of 17β-estradiol (Vagifem®) to post-menopausal women once-weekly or twice weekly for more than 3 months (See page 23, abstract; page 24 and 25, Subjects and Methods Section). Mettler and Olsen also teaches that the 17β-estradiol treatment is effective in relieving the symptoms of atrophic vaginitis such as vaginal dryness (See page 28, second paragraph, also Table 2).

Vagifem monograph teaches that the inert excipient of Vagifem tablet containing hydroxypropyl methylcellulose (hypromellose), lactose monohydrate, maize starch, and magnesium stearate (page 1, col. 1). Vagifem monograph also teaches that the film coating of the tablet containing hydroxypropyl methylcellulose (hypromellose) and polyethylene glycol (Macrogel 6000).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ estradiol, in a tablet dosage form containing 53.7mg

hypromellose, about 17.9mg lactose monohydrate, about 8 mg maize starch, and about 0.4 mg magnesium stearate and coated with a film consisting of about 0.5mg hypromellose and about 0.06 mg Macrogel 6000, to treat atrophic vaginitis. It would have been obvious to one of ordinary skill in the art at the time the invention was made to adjust the dosage frequency to the herein claimed dosage frequency.

One of ordinary skill in the art would have been motivated to employ estradiol, in a tablet dosage form containing 53.7mg hypromellose, about 17.9mg lactose monohydrate, about 8 mg maize starch, and about 0.4 mg magnesium stearate and coated with a film consisting of about 0.5mg hypromellose and about 0.06 mg Macrogel 6000, to treat atrophic vaginitis. Vagifem is known to be useful in treating atrophic vaginitis, and the herein claimed dosage of estradiol is also known to be effective in treating atrophic vaginitis. Possessing the teachings of the cited prior art, one of ordinary skill in the art would have been reasonably expected to employ Vagifem tablet, in a lower dose to avoid systemic side effects, in a method of treating atrophic vaginitis.

One of ordinary skill in the art would have been motivated to adjust the dosage frequency to the herein claimed dosage frequency. The optimization of result effect parameters (e.g., dosage range, dosing regimens to avoid side effects) is obvious as being within the skill of the artisan.

Response to Arguments

Applicant's arguments filed February 25, 2004 citing paragraphs 3-6 in declaration by Dr. Nachtigall have been fully considered but they are not persuasive. The arguments are responded in the following paragraphs.

In paragraph 3, declaration by Dr. Nachtigall, it is stated that in her opinion, no clinical practitioner would employ 10μg estradiol once or twice weekly to effective treat atrophic vaginitis. Such arguments have been considered, but are not found persuasive. Examiner notes that Dr. Nachtigall's opinion is partly based on the absence of clinical experience that could have supported such use of low dose estradiol as effective in treating atrophic vaginitis (See the last line of paragraph 3). However, Meignant clearly teaches the employment of low dose 17-β-estradiol, i.e., 5μg or 2.5μg, locally to treat atrophic vaginitis (See col. 4, lines 27-36; also col. 6, lines 38-54). Meignant discloses such low dose of estradiol would have been effective in treating atrophic vaginitis and at the same time, minimizing systemic side effects.

In paragraph 4, declaration by Dr. Nachtigall, it is stated that there is no clinical data at all relating to the efficacy of treating atrophic vaginitis using low dose estradiol and therefore, one of ordinary skill in the art would not have been motivated to employ the herein claimed regimen for treating atrophic vaginitis. The arguments have been considered, but are not found persuasive. As discussed above, Meignant discloses such low dose of estradiol would have been effective in treating atrophic vaginitis and at the same time, minimizing systemic side effects. Although Meignant does not expressly disclose the effectiveness of the herein claimed low dose of estradiol, the inventors in Meignant clearly envision 2.5-15μg of estradiol, which encompassed the herein claimed

dosage, as effective in treating atrophic vaginitis. Examiner notes that the rejection is not an anticipatory rejection. It is an obviousness rejection. Therefore, taken the teachings of the cited prior arts together, one of ordinary skill in the art would have been motivated to employ the herein claimed regimen of estradiol in the method of treating atrophic vaginitis.

Applicant's arguments in paragraph 5, declaration by Dr. Nachtigall averring "soft capsule are inferior to tablets in that administration of soft capsules results in erratic release of their estradiol contents, in contrast with vaginal tablets which are know [sic] to release in a more constant manner" (in paragraph 5, last sentence) have been considered, but are not found persuasive. Examiner notes that applicant's response filed February 25, 2004 does not provide factual evidences to demonstrate that soft capsules have an erratic release when compared to that of tablets. Furthermore, the secondary reference (i.e., Mettler and Olsen) actually teaches estradiol released in a tablet dosage form although the dosage disclosed in Mettler and Olsen is not the same as that of herein claimed. Optimizing the result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary.

Applicant's arguments in paragraph 6, declaration by Dr. Nachtigall averring unexpected success of employing the herein claimed low dose of estradiol have been considered, but are not found persuasive. As discussed above, Meignant clearly discloses 2.5-15μg of estradiol, which encompassed the herein claimed dosage, as effective in treating atrophic vaginitis. There is no data as to comparing the dosage

forms of Meignant and that of the instant invention to demonstrate unexpected benefits of employing the herein claimed dosage forms. Therefore, absent evidence to the contrary, possessing the teachings of the cited prior art, one of ordinary skill in the art would have reasonably expected to employ the herein claimed estradiol regimen to treat atrophic vaginitis.

Applicant's arguments averring the cited prior art's failure to motivate one of ordinary skill in the art to employ the herein claimed regimen to treat atrophic vaginitis by citing Santen et al. (Menopause, 2002, 9(3):179-187 provided by the applicant) have been considered, but are not found persuasive. The dosage of estradiol for treatment of atrophic vaginitis is taught in Meignant. Therefore, possessing the teachings of Meignant, one of ordinary skill in the art would still be motivated to employ low dose estradiol, the same as herein recited, to treat atrophic vaginitis.

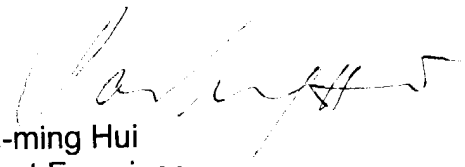
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



San-ming Hui
Patent Examiner
Art Unit 1617